Relationship between preeclampsia umbilical blood flow and perinatal outcome

Prof. Abdulrazak H. Alnakash [*], Dr. Zena Abass Mushina [**]

[*] M.B.Ch.B, F.IC.O.G, C.A.B.O.G, Alkindy Medical College / Baghdad University, Al-Elwiya Maternity Teaching Hospital
[**] M.B.Ch.B , Al-Elwiya Maternity Teaching Hospital

***Abstract*- Background:** Doppler indices of the umbilical artery are used as indicator of fetal well being that permit early detection of fetal compromise and avoid delaying in the management.

Study design: A prospective multiple logistic regression analysis studies**.**

Objective: To compare Doppler parameters of umbilical artery including pulsatility index (PI) and resistance index (RI) and systolic diastolic ratio [S/D] in patients suffering from preeclampsia with those having normal pregnancies and to evaluate the diagnostic characteristics of these parameters in fetal outcome.

Materials and Methods: One hundred singleton pre-eclamptic women at their term (50 with mild & 50 with severe preeclampsia) and 50 women with normal pregnancy were included in the study & subjected to doppler study of the umbilical artery where resistance index , pulsatility index & systolic diastolic ratio were measured using doppler ultrasound (Acuson x3oo) at Al-Elwiya Maternity Teaching Hospital during the period from May 2013 to July 2014. Fetal outcome (fetal weight, Apgar score and Neonatal Care Unit admission NCU) were compared in the two groups and diagnostic characteristics of the Doppler indices were determined. The data are arranged on questionnaire papers and then subjected to statistical analysis.

Results: Mean of pulsatility index (1.32), resistance index (0.77) and systolic diastolic ratio (3.38) in preeclamptic patients were significantly higher than normal group (PI 0.97, RI 0.64&S\D ratio 2.68), elevated Doppler indices were found to be associated with worse fetal outcome (low birth weight, Apgar score and higher NCU admission). Besides, those with severe preeclampsia showed significantly higher values of (PI 1.52, RI 0.83& S\D ratio 3.86) compared to those with mild preeclampsia (PI 1.24, RI 0.74 & S\D ratio 2.90). For PI, the cut-off of ≥0.98 yielded the highest sensitivity and specificity. Also, RI of 0.64 acquired a sensitivity of 100% and specificity of 44% and same result for S/D ratio.

Conclusion: Umbilical artery pulsatility index, resistance index and S/D ratio increase in preeclampsia and these changes tend to be greater in severe preeclampsia and with worse fetal outcome (low birth weight, Apgar score and higher NCU admission) the cut-off values were 0.98 for PI and/or 0.64 for RI.

***Index Terms*-** perinatal outcome, preeclmpcia, Doppler ultrasound, umbilical artery

I. Introduction

Doppler of the umbilical artery has been used extensively for assessing downstream circulatory impedance (i.e., resistance to pulsatile flow) (1,2). Doppler waveform analysis is usually based upon the following characteristics of the maximum frequency shift envelope: Peak systolic frequency shift value (S) End-diastolic frequency shift value (D). Average frequency shift value over the cardiac cycle (A) These three values are used to develop indices that reflect the pulsatility of the Doppler waveform reflecting the dynamic changes in the circulation through the cardiac cycle. The most commonly used obstetrical applications are the peak systolic frequency shift to end-diastolic frequency shift ratio, (S/D) (1) and the resistance index (RI), which represents the difference between the peak systolic and end-diastolic shift divided by the peak systolic shift (3). Analysis of Doppler waveforms from an arterial source yields information about downstream impedance to flow: the Doppler index (DI) worsens with increasing pathology of fetoplacental vascular system (4). Abnormal fetal placental angiogenesis characterized by sparse, elongated, uncoiled, and less ramified terminal capillary loops are seen in pregnancies complicated by growth restriction and abnormal umbilical arterial Doppler in preeclampsia (5,6).

As the stress intensifies and/or lengthens, the fetus mobilizes defensive responses that include preferential preservation of fetal growth over placental growth, changes in fetal movement pattern, deceleration of the fetal growth rate, and, eventually, chronic hypoxia and acidosis. The primary fetal hemodynamic response to this deprivation involves redistribution of blood flow to the brain, heart, adrenals, and placenta at the expense of flow to muscles, viscera, skin, and other less critical tissues and organs (7). Changes in blood flow impedance in the fetal regional circulations underlie this phenomenon. Doppler ultrasound demonstrates these circulatory changes associated with fetal compromise and allows perinatal prognosis. The sequence of changes in fetal heart rate, Doppler findings, and other biophysical parameters during progressive fetal compromise reflect the fetal homeostatic response to chronic hypoxia (8). Abnormal elevation of Doppler indices precedes loss of fetal heart rate variability and reactivity, eventually leading to decline and loss of fetal breathing and body movements (9,10).

Absence of end-diastolic flow velocity (AEDV) or reversal of end-diastolic flow velocity (REDV) is associated with markedly adverse perinatal outcome, particularly a high perinatal mortality rate with a higher prevalence of chromosomal

abnormalities (especially trisomy 13, 18, and 21) and congenital anomalies (11,12).

The aim is to study the relation between preeclampsia umbilical blood flow changes and pregnancy outcome (fetal weight, Apgar score and NCU admission).

II. Patients and methods

The study population consisted of 100 preeclamptic singleton pregnants (50 with severe & 50 mild) and 50 women with normal pregnancies served as control, the patients were collected while attending Al-Elwiya Maternity Teaching hospital in Baghdad from 1st May 2013 to end of July 2014. Their gestational age was more than 36 weeks in both groups and was established by the accurate menstrual history and an ultrasonographic examination report before 20th week of pregnancy (growth restriction and pregnant with medical disorders like diabetes had been excluded from the study).

Preeclampsia was diagnosed when blood pressure ≥140/90 after 20th week of gestation with appropriate cuff and supine position in at least two occasions 4 hours apart and random proteinuria of ≥+1 or 24hours proteinuria more than 300m. Rise of blood pressure to ≥160/110 with a proteinuria of >+2 or 24 hours proteinuria of >2 gram, and presence of headache, epigastric pain, blurred vision, pulmonary edema, abnormal liver and renal function test was considered as severe preeclampsia. Questionnaire form was designed for the patients where the demographic data (Age, parity, LMP, medical diseases) and the doppler indices readings were recorded for study analysis. Cases of intra uterine growth restriction, fetal anomalies, twin pregnancy, and underlying chronic disease were excluded from the study. All the participants underwent a routine ultrasonogrphic scan before the Doppler examination by which gestational age was confirmed and presence of intrauterine growth restriction and fetal anomaly were excluded. Doppler ultrasound examination of the umbilical artery was performed on them in the left lateral recumbent position using a color Doppler system (Acuson x300). The umbilical artery was identified and flow velocity waveforms were obtained from a free-floating.

Loop of the cord during fetal quiescence the sample volume was 2–4 mm and the smallest possible velocity scale and lowest required pulse repetition frequency were used. Recordings were made when at least three nearly identical consecutive waveforms were visible on the screen. All sonographic studies were performed by the same expert examiner who was not aware of the study design. Doppler parameters including pulsatility index (PI) , resistance index (RI) and(S/D) ratio were calculated by the dedicated software supplied within the Doppler equipment. The average value of at least two waveforms was considered as the final measurement.

Out of 100 preeclamptic patients, 50 with mild PET, 25 of them, their pregnancy was terminated by caesarean section either because they developed severe PET, in 16 pregnants, during the study period or fetal distress during labor in 9 of them. The remaining (25 women) delivered by vaginal delivery under our strict supervision.

While those with severe PET (50 women), 46 were delivered by Caesarean section either because maternal distress in 36 or for fetal distress in 10 & only 4 pregnants in this group had controlled vaginal birth.

The newborns were examined by pediatrician for Apgar scoring & fetal body weight. Regarding neonatal unit admission, 13 babies of those with severe preeclampsia were admitted to the unit for more than 24 hr (2-3 days) while only10 babies of those with mild PET and only 2 babies of the control group required admission to the neonatal unit.

III. Statistical analysis

Independent t-test was used for continuous variables with normal distribution.

Mann-Whitney test was used to calculate the differences between the two groups in case of nonparametric data. Receiver Operating Characteristic curve analysis was performed and the area under the curve (AUC) with corresponding confidence intervals (CIs) was calculated. Diagnostic characteristics of the indices were determined by means of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and positive likelihood ratio (LR+). SPSS (Statistical package for social perform data sciences) was used to analysis

IV. Results

Table 1: Describes basic characteristic of normal and preeclamptic groups (mild and severe) by their age, gestational age, gravity and living child which are shown by mean and standard deviation to all 150 pregnant (50 normal, 50 mild and 50 severe preeclampsia).

Table 1. Basic characteristics of the studied groups

Group characteristic	Normal pregnancy	Mild Preeclampsia	Sever preeclampsia
Age (years)	25.6(4.3)	26.4(4.4)	27.2(3.2)
Gravity (number)	2.1(1.1)	1.5(0.9)	1.9(1.2)
Living child (number)	0.8(0.9)	0.4(0.6)	0.3(0.5)

Number are shown as mean(SD)

Table 2: Describes umbilical artery indices of normal and preeclamtic (mild and severe) groups including [pulsatility index, resistance index and systolic/diastolic ratio] by mean and standard deviation of the results and analyses the results by P-value between normal pregnancy and total preeclampsia value and also between mild and sever preeclampsia. So it shows increase of umbilical artery indices in total preeclamptic group in compare to normal pregnancy group ,which shows PI[1.32(0.23)] in total preeclampsia compare to [0.97(0.18)] of normal group, Also in RI [0.77(0.09)] in total preeclampsia compare to [0.64(0.08)] of normal pregnancy group, In S/D ratio also there is increase in preeclamptic group [3.38(0.82)] in compare to normal pregnancy group [2.68(0.16)].P-value in

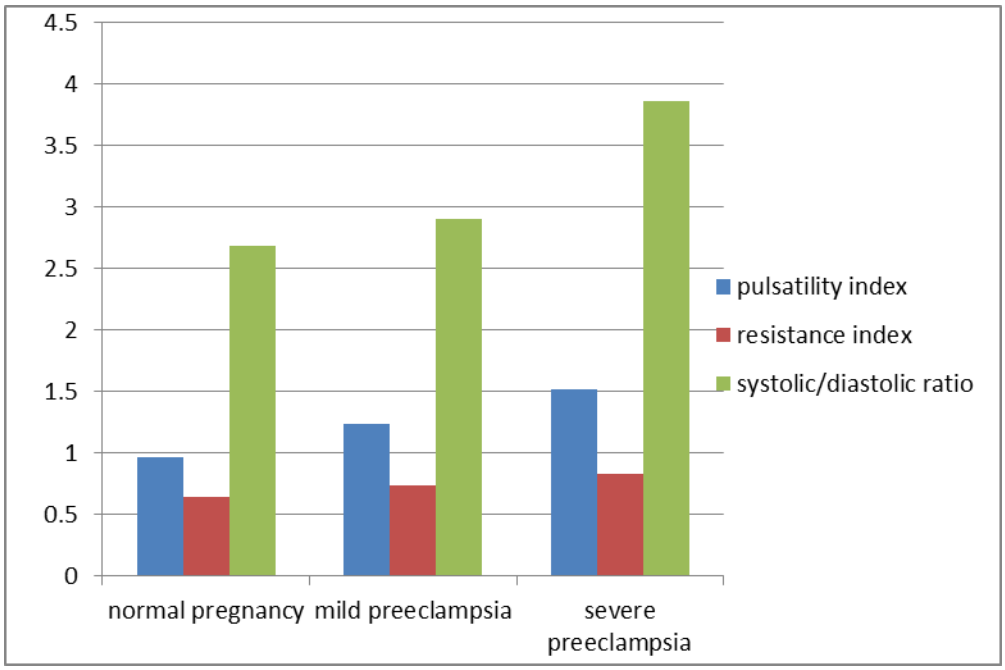
study of all three indices results in normal pregnancies and total preeclampsia was <0.001 which have level of significance. While P-value of all three indices in mild and sever preeclampsia was< 0.05.

Table 2. Umbilical artery indices of the studied groups

Index	Normal pregnancy	Total preeclampsia	P-value	Mild preeclampsia	Severe preeclampsia	P-value
Pulsatility index	0.97(0.18)	1.32(0.23)	<0.001	1.24(0.17)	1.52(0.25)	<0.05
Resistance index	0.64(0.08)	0.77(0.09)		0.74(0.08)	0.83(0.07)	
Systolic /diastolic ratio	2.68(0.16)	3.38(0.82)		2.90(0.24)	3.86(1.41)	

Numbers are shown as mean (SD).

Figure1: Shows the differences in Doppler ultrasound indices between normal pregnancy and mild and severe preeclampsia where there is increase of the indices in preeclamptic groups in compare to normal pregnancy group.



Number shown by the (mean)

Table 3: Diagnostic characteristics of pulsatility and resistance index for predicting preeclampsia at different cut-offs.by comparison of our cut-off value (PI: 0.98) and (RI: 0.64) with other cut-off.

Index	Cut-offs values	Se (%)	SP (%)	PPV (%)	NPV (%)	LR+
	0.58	100	1.3	25.3	100	1.01
	0.78	100	17.3	28.7	100	1.21

Pulsatility Index						
	0.98	100	53.3	41.7	100	2.14
	1.18	64	85.3	59.3	87.7	4.36
Resistance Index	0.44	100	1.3	25.3	100	1.01
	0.54	100	9.3	26.9	100	1.10
	0.64	100	44	37.3	100	1.79
	0.81	28	100	100	80.6	NA

Se:senitivity ; SP:specificity ; PPV:positive predictive value ;NPV:negative predictive value ;LR+:positive likelihood ratio ;NA:not applicable

Table 4: Describes the number and percentage for indications of termination the pregnancy (maternal distress ,fetal distress & normal labor) in mild preeclamptic (50pregnant) and severe preeclamptic (50 pregnant) which shows increase the indication of termination because maternal distress 52 (52%), while fetal distress 19(19%) and by normal labor 29 (29%).

Table 4. indications for termination of pregnancy

Preeclamptic groups	**Termination cause**		**Normal labor**	**total**
	Maternal distress	**Fetal distress**		
Mild preeclampsia	16(16%)	9(9%)	25(25%)	50(50%)
Severe preeclampsia	36(36%)	10(10%)	4(4%)	50(50%)
total	52(52%)	19(19%)	29(29%)	100(100%)

Number shown as number (%)

Table 5: Describe fetal outcome of normal group (50pregnant) and preeclamptic groups (50 mild preeclampsia and 50 severe preeclampsia) including fetal weight, APGAR score in one minute and 5 minute by mean and standard deviation. NCU admissions by number and percentage of each 50 pregnancies group (normal, mild and severe) .which shows decrease in fetal weight in severe preeclamptic group { 2.18(0.25) } and mild {2.9(0.22)} in compare with fetal weight of normal pregnancies {3.1(0.23)}, and decrease in APGAR score of sever preeclampsia {2.18(0.25)in 1min & 5(0.55)in 5 min} in compares with normotensive group {5.3(0.96) in one minute &7.78(0.87) in 5 minute} . NCU admissions there is increase in fetal admissions of severe preeclamtic pregnancies [13 of 50 fetus(26%)] and mild preeclamptic group [10 of 50 fetus (22%)] in compare to normal pregnancy [2 of 50 fetus (4%)].

Table 5. fetal outcome

groups	**Fetal body Weight Mean(SD)**	**APGAR score Mean(SD)**		**NCU Admissions Number(%)**
		1 min	**5 min**	
Normal pregnancy	3.1(0.23)	5.3(0.96)	7.78(0.87)	2(4%)
Mild Preeclampsia	2.9(0.22)	3.75(1.23)	7.3(1.10)	10(22%)
Severe Preeclampsia	2.18(0.25)	2.8(0.41)	5(0.66)	13(26%)

V. DISCUSSION:

It's very important to predict fetal distress and outcome in order to plan early interference and avoid delaying management. The results obtained from the study showed higher umbilical pulsatility, resistance indices and S\D ratio and worse fetal outcome (low birth weight, Apgar score, higher NCU admission) in pregnant with preeclampsia compared with normal pregnancies reflecting high resistance in placental circulation in preeclampsia. The findings obtained from this work go with the study performed by **Chen *et al***. (13) who reported a prospective longitudinal population-based study of relationship between preeclampsia umbilical blood flow and perinatal outcome , not only a higher pulsatility index but also a significantly greater PI in severe cases of preeclampsia compared to mild cases, S/D, PI, and RI all tended to increase with the severity of preeclampsia, and these indices were significantly higher in patients with severe preeclampsia than in normal group ($P<0.01$) but they showed no significant differences between mild preeclampsia group and the normal group ($P>0.05$). The average birth weight of the newborns, Apgar scores were significantly lower ($P<0.01$), and the incidence of fetal growth restriction (FGR) and perinatal mortality significantly higher in severe preeclampsia group than in the control group ($P<0.01$). No significant differences were found in these parameters between the mild preeclampsia and the control groups ($P>0.05$) (48). On the other hand**, Ozeren *et al*** (14) reported who study on umbilical and middle cerebral artery Doppler indices in patients with preeclampsia, significant differences were found between normal pregnancies and preeclampsia patients; all the mean Doppler indices were different from those of the normal pregnancies. The UA S/D had the highest sensitivity (88%) and diagnostic accuracy (94%) in predicting the adverse perinatal outcome & their study goes with our finding. **Acharya *et al.*** (15) studied doppler indices in second half of pregnancy, serial measurement of umbilical artery Doppler indices in 130 low risk pregnancies obtained a 50th percentile and 95th percentile umbilical artery PI of 0.88 and 1.22, respectively whereas, 50th percentile RI calculated to be 0.60 and 95th percentile RI was 0.74 in 33rd week of gestation.

The difference in the methods and the number of umbilical artery waveforms studied can account for the different values reported in various studies. Doppler indices from the present study show a continuous reduction throughout the second half of pregnancy without any plateau or increase near term. There was a significant negative association between Doppler indices and placental weight and neonatal birth weight, but not with gender. The umbilical artery pulsatility index, resistance index, and systolic diastolic ratio were 10.5%, 6.8 %, and 13.0 %, respectively. According to **Skotnicki *et al*** (16) Doppler examinations are highly useful in the prediction of birth status of the newborn if the specific conditions and appropriate range of the examination are maintained, i.e.: 1) examination must be multivascular, 2) it should involve cerebral artery, parenchyma resistance vessels (for example renal artery), umbilical artery and vein, intramural uterine vessels (for example arcuate or spiral artery), 3) among blood flow parameters not only standard indices (S/D, RI, PI), but also arterial blood flow waves velocity, specific flow and transverse section field should be considered. In **Viero *et al*** (17) pregnancies with abnormal fetoplacental blood flow (defined by absent or reversed end-diastolic flow velocities [ARED] in the umbilical arteries) have a high perinatal mortality. In **Harman *et al.*** (18) umbilical artery Doppler indices reflect downstream placental vascular resistance, strongly correlated with intrauterine growth restriction and the multisystem effects of placental deficiency. Abnormalities are progressive, with reduction, loss, and finally a reversal of diastolic flow. In **Molvarec *et al*** (19) abnormal fetal flow was defined as either signs of centralization of the fetal circulation or diastolic block or reverse flow in the umbilical artery or descending aorta; this was a criterion for delivery. Fetal outcomes were intrauterine growth restriction and birth before 37 weeks of pregnancy. In **Alfirevic *et al*** (20) abnormal blood flow patterns in fetal circulation detected by high Doppler indices of the umbilical artery may indicate poor fetal prognosis. It is also possible false positive Doppler ultrasound findings could encourage inappropriate early delivery. All these studies go with our study and in consistence with these results. Umbilical Doppler indices were found to be higher in preeclampsia than in normal pregnancy &significantly higher in severe preeclampsia with worse fetal outcome (low birth weight, low Apgar score &higher NCU admission). Furthermore we report cut-off values 0.98 for PI and 0.64 for RI, which might be used as sensitive marker to detect early signs of fetal distress.

VI. CONCLUSION

Umbilical artery Doppler indices increase in preeclampsia and these changes tend to be greater in severe preeclampsia and worsen the fetal outcome (low birth weight, low Apgar score & high NCU admission). Umbilical artery PI and RI seem to be more appropriate in excluding preeclampsia as a cause of placental insufficiency& predicting of fetal outcome and we found the cut-off values 0.98 for PI and 0.64 for RI, to rule-out the disease. This helps early detection of fetal compromise & prevents delay in management.

REFERENCES

[1] Detti L, Akiyama M, Mari G. Doppler blood flow in obstetrics.Curr Opin Obstet Gynecol 2002; 14:587-593

[2] Mukhopadhyay A, Sharma P, Dasgupta S, Sharma PP, Ghosh TK. Prediction of pre-eclampsia. comparative analysis of two screening tests. J Indian Med Assoc 2012; 110:546-547.

[3] Harman CR, Baschat AA. Comprehensive assessment of fetal wellbeing. which doppler tests should be performed? Curr Opin Obstet Gynecol 2003; 15:147-157.

[4] Espinoza J, Romero R, Nien JK, Gomez R, Kusanovic JP, Goncalves LF, Medina L, Edwin S, Hassan S, Carstens M, Gonzalez R. Identification of patients at risk for early onset and/or severe preeclampsia with the use of uterine artery doppler velocimetry and placental growth factor. Am J Obstet Gynecol 2007; 196:326.

[5] Docket K, Harrington D. Risk factors for pre-eclampsia at antenatal booking.systematic review of controlled studies. BMJ 2005; 330:565.

[6] Kaaja R. Predictors and risk factors of pre-eclampsia. Minerva Ginecol 2008;60:421-429.

[7] Westergaard HB, Langhoff-Roos J, Lingman G, Marsal K, Kreiner S. A critical appraisal of the use of umbilical artery doppler ultrasound in high-risk pregnancies. use of meta-analyses in evidence-based obstetrics. Ultrasound Obstet Gynecol 2001;17:466-476.

[8] Bahlmann F, Reinhard I, Krummenauer F, Neubert S, Macchiella D, Wellek S. Blood flow velocity waveforms of the fetal middle cerebral artery in a

normal population. reference values from 18 weeks to 42 weeks of gestation. J Perinat Med 2002; 30:490-501.

[9] Ebbing C, Rasmussen S, Kiserud T. Middle cerebral artery blood flow velocities and pulsatility index and the cerebroplacental pulsatility ratio. longitudinal reference ranges and terms for serial measurements. Ultrasound Obstet Gynecol 2007; 30:287-296.

[10] Morris RK, Malin G, Robson SC, et al. Fetal umbilical artery Doppler to predict compromise of fetal/neonatal wellbeing in a high-risk population. systematic review and bivariate meta-analysis. Ultrasound Obstet Gynecol 2011; 37:135.

[11] Maulik D, Yarlagadda AP, Youngblood JP, Willoughby L. Components of variability of umbilical arterial Doppler velocimetry--a prospective analysis. Am J Obstet Gynecol 1989; 160:1406.

[12] Bilardo CM, Nicolaides KH, Campbell S. Doppler measurements of fetal and uteroplacental circulations. relationship with umbilical venous blood gases measured at cordocentesis. Am J Obstet Gynecol 1990; 162:115.

[13] Chen J, Yu YH, Wang ZJ, Qin W, Zhang Q. Relationship between preeclampsia umbilical blood flow and perinatal outcomes. Nan fang yi ke da xue bao 2009; 29: 745-746.

[14] Ozeren M, Dinç H, Ekmen U, Senekayli C, Aydemir V. Umbilical and middle cerebral artery Doppler indices in patients with preeclampsia. Eur J Obstet Gynecol Reprod Biol 1999; 82: 11-16.

[15] Acharya G, Wilsgaard T, Berntsen GK, Maltau JM, Kiserud T. Doppler indices in the second half of pregnancy. Am J Obstet Gynecol 2005; 192: 937.

[16] Skotnicki MZ, Flig E, Urban J, Hermann T. Doppler examinations in the prognosis of birth status of the newborn. Med Sci Monit 2000; 6:611-615.

[17] Viero S, Chaddha V, Alkazaleh F, Simchen MJ, Malik A, Kelly E, Windrim R, Kingdom JC. Prognostic value of placental ultrasound in pregnancies complicated by absent end-diastolic flow velocity in umbilical arteries. Placenta 2004; 25:735-741.

[18] Harman CR, Baschat AA. Comprehensive assessment of fetal wellbeing. which doppler tests should be performed? Curr Opin Obstet Gynecol 2003; 15:147-157

[19] Molvarec A, Gullai N, Stenczer B, Fugedi G, Nagy B, Rigo J Jr. Comparison of placental growth factor and fetal flow doppler ultrasonography to identify fetal adverse outcomes in women with hypertensive disorders of pregnancy, an observational study.BMC Pregnancy Childbirth 2013; 13:161.

[20] Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev 2010; 75:29.

AUTHORS

First Author – Prof. Abdulrazak H. Alnakash M.B.Ch.B, F.IC.O.G, C.A.B.O.G, Consultant OBGYN, Alkindy Medical College / Baghdad University, Al-Elwiya Maternity Teaching Hospital, razaknakash@yahoo.com, +964 7901 311 564
Second Author – Dr. Zena Abass Mushina M.B.Ch.B, Registrar and candidate of Arab Board , Al-Elwiya Maternity Teaching Hospital